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Tetra-Amelia and Splenogonadal Fusion in Roberts Syndrome

Thomy J.L. de Ravel,[1*] Matthew D. Seftel,[1] and Colleen A. Wright[2]

[1]*Department of Human Genetics, The School of Pathology, The South African Institute for Medical Research and University of the Witwatersrand, Johannesburg, South Africa*

[2]*Department of Anatomical Pathology, The School of Pathology, The South African Institute for Medical Research and University of the Witwatersrand, Johannesburg, South Africa*

Roberts-SC phocomelia syndrome comprises limb deficiencies of variable severity, facial clefts, and other anomalies. Tetra-amelia may also be associated with facial clefts and similar anomalies. We report on a female infant with severe tetra-amelia, micrognathia, cleft palate, splenogonadal fusion, and premature centromere separation. We propose that this represents the severe expression of the Roberts-SC phocomelia syndrome. Am. J. Med. Genet. 68:185–189, 1997

KEY WORDS: splenogonadal fusion; tetra-amelia; premature separation of centromeres; Roberts syndrome

INTRODUCTION

Congenital limb deficiencies have a birth prevalence of 0.55 per 1,000 [Evans et al., 1994] and may be isolated or associated with multiple malformations. The autosomal recessive Roberts-SC phocomelia syndrome is clinically characterised by phocomelia of variable severity, facial clefts, and other anomalies. Amelia (complete absence of a limb) has a birth prevalence of 0.01 per 1,000 births, over 50% being associated with multiple malformations [Evans et al., 1994]. A number of cases of tetra-amelia have been reported associated with midfacial clefts, lung hypoplasia, and other anomalies [Başaran et al., 1994].

Splenogonadal fusion was first reported in 1883 by Bostroem, and its association with limb defects, micrognathia, and other congenital anomalies noted by Pommer in 1889 [reported in Carragher, 1990]. Putschar and Manion [1956] divided the cases into those with "continuous splenic-gonadal fusion" in which a continuous cord-like structure connects the spleen and the gonadal-mesonephric structures, and the "discontinuous" type lacking the connection. The latter may be a special variant of accessory spleens. The continuous form of splenogonadal fusion has been associated with limb and palatal defects, micrognathia, and various other anomalies [Carragher, 1990].

Lipson [1995] reported what he described as the 20th case of splenogonadal fusion associated with congenital limb deficiencies and, because the parents were consanguineous, suggested the possibility of autosomal recessive inheritance of this condition. Previous cases were regarded as sporadic.

Carragher [1990] reviewed 123 cases of splenogonadal fusion, of which 116 were in males and only 7 in females. The continuous type was found in 71 cases (56%), and these were more frequently associated with other congenital anomalies than those in the discontinuous group (23 vs. 1 case).

Twenty of the seventy-one cases with the continuous form had limb deficiencies. Although Carragher [1990] reports that all cases of splenogonadal fusion in females were of the continuous type, Walther et al. [1988] had commented on one female with the discontinuous type. The low number of females reported may be an ascertainment bias, as they present less frequently with clinical signs than do the male individuals.

Premature centromere separation (PCS) consists of "puffing" or "repulsion" of the constitutive heterochromatin and is most clearly and frequently seen in chromosomes 1,9,16, and Y, as well as at the nucleolar organising regions of the acrocentric chromosomes. However, all chromosomes have been described as showing the phenomenon, which is best demonstrated using the C band staining technique. Seventy-nine percent of individuals with the Roberts-SC phocomelia syndrome show PCS. They are clinically indistinguishable from the 21% who do not have PCS [Van Den Berg and Francke, 1993]. Allingham-Hawkins and Tomkins [1995] suggested that these two groups of patients belong to different complementation groups.

Tetra-amelic individuals are not routinely investigated for PCS. We have found one case report of tetra-amelia in which PCS was found [Paulson et al., 1989] and two cases in which the investigation was carried

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*Correspondence to: Dr. Thomy J.L. de Ravel, Department of Human Genetics, The South African Institute for Medical Research, P.O. Box 1038, 2000 South Africa.

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out and reported to be negative [Başaran et al., 1987; Rosenak et al., 1991]. We report a case of a female neonate with tetra-amelia, micrognathia, a cleft of the soft palate, pre-auricular pits, a large anterior fontanelle, pulmonary hypoplasia, and splenogonadal fusion of the continuous type, in which PCS was present. We propose that some cases of tetra-amelia represent the severest expression of the Roberts-SC phocomelia syndrome and that investigations for PCS be carried out routinely in all such cases. We conclude that our case represents the first report of splenogonadal fusion occurring in Roberts syndrome.

CLINICAL REPORT

An 18-year-old woman presented at the delivery ward for the first time at term gestation with her first pregnancy. She had no antenatal care or investigations. She gave no history of alcohol, drug, or other substance use during the pregnancy. Consanguinity was not reported. A female infant was delivered by breech extraction. She weighed 1,690 g with a crown-rump length of 28 cm and a head circumference of 33 cm. The anterior fontanelle was 45 × 60 mm and connected via a 13 mm wide sagittal suture to the intermediate and posterior fontanelles. Haemangiomata were evident in the supraorbital and nasal areas. Corneal opacities were not noted. A small hirsute pre-auricular pit was present bilaterally. Micrognathia (Fig. 1) and a cleft of the soft palate were present. The neck was short.

Tetra-amelia was evident (Fig. 2). A small dimple was present at the right, and a nubbin of soft tissue at the left "thigh area" (Fig. 3). Clitoromegaly was present (Fig. 4). The anus was patent. A chest radiograph documented cervical vertebral anomalies and 11 pairs of thin ribs. The infant died of respiratory insufficiency a few hours after birth.

The rating system for quantitative severity of Roberts syndrome resulted in a total score of 7 using five criteria (i.e., a high +1.4 rating), namely, phocomelia of upper limbs (+2), phocomelia of lower limbs (+2), survival (+1), palatal anomalies (+1), and other craniofacial anomalies (+1 for micrognathia) [Van Den Berg and Francke, 1993].

At autopsy the gestational age was estimated (on head circumference) to be about 38 weeks. The combined lung weight was 30 g (expected 40.6 ± 17.1 g). The lung/estimated body weight ratio was 0.011 [normal over 0.012, Wigglesworth and Singer, 1991] indicating mild pulmonary hypoplasia.

The spleen weighed 5 g (expected weight 9.5 ± 3.5 g). A cord ran from the spleen along the left paracolic gutter and attached to the left ovary situated in the normal anatomical position (Fig. 5). No accessory spleens were found.

The brain showed evidence of polymicrogyria; histologic study demonstrated poor migration of neurons from the peri-ventricular to the cortical zones. Further autopsy findings were normal.

Karyotype was 46,XX; premature centromere separation was present in about 50% of metaphase spreads. Chromosomes of the C group most commonly displayed the phenomenon, followed by the acrocentrics (Fig. 6).

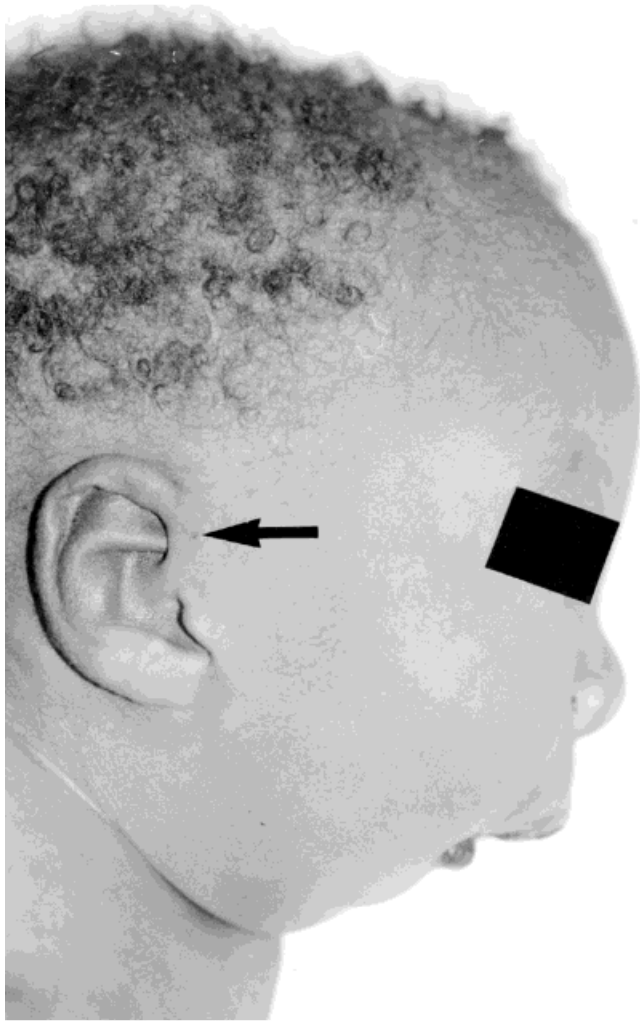

Fig. 1. Pre-auricular pit (arrow) and micrognathia.

DISCUSSION

Splenogonadal Fusion

At about the fifth week of embryonic life, the spleen develops as a trilobar mesodermal growth of the left dorsal mesogastrium. As the gut rotates in the ensuing weeks, the developing spleen comes into close contact with the urogenital fold containing the gonadal mesoderm. Two layers of peritoneum thus usually separate the spleen from the gonad. This close association is normally lost after the 8th week of embryonic development as the gonad descends. Splenogonadal fusion occurs between the 5th and 8th week. The cause is as yet undetermined. It has been proposed that it may be due to the intimate intermingling of the circulation of the two organs [von Hochstetter as reported in Putschar and Manion, 1956]. Alternatively, it could be the result of a breakdown of the two layers of peritoneum between these two developing organs secondary, perhaps, to a vascular accident which would facilitate fusion. In cases such as the one described here, the slow cell turnover rate may positively influence this process.

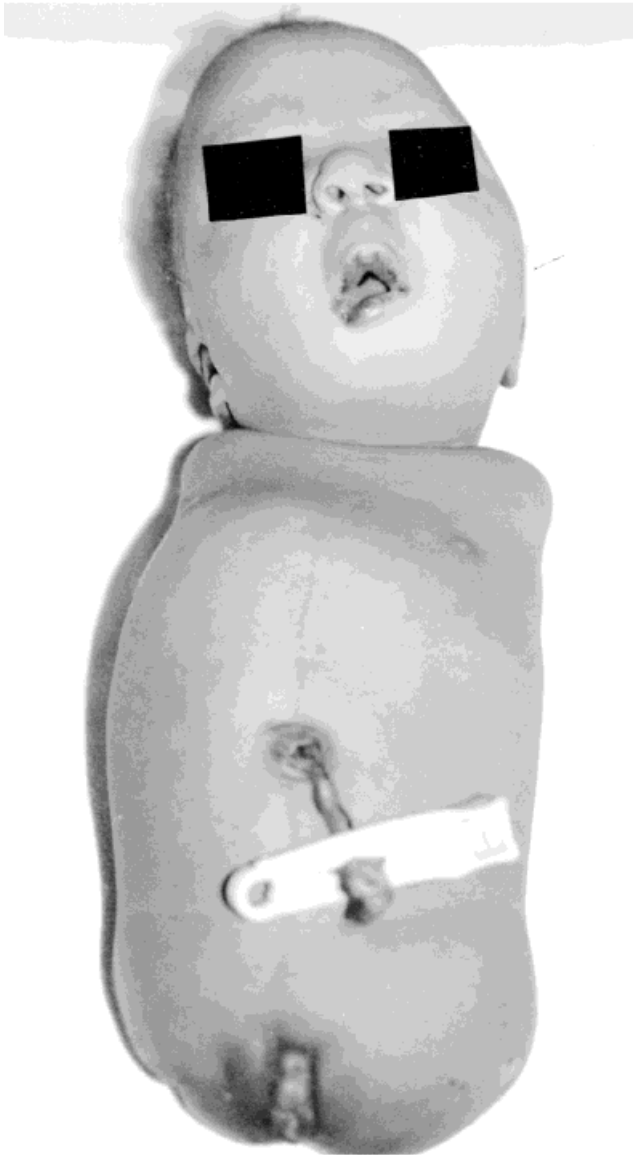

Fig. 2. Tetra-amelia.

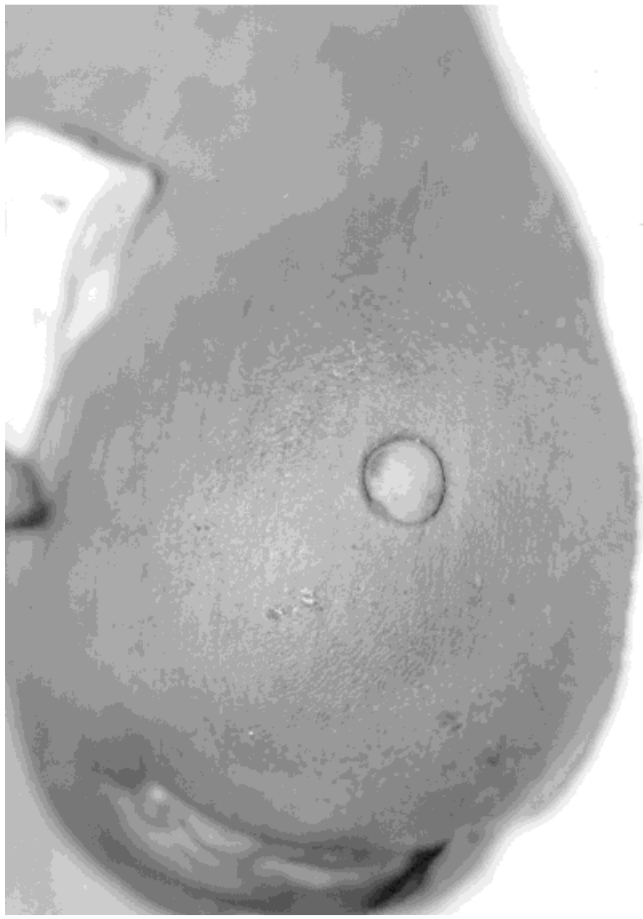

Fig. 3. A nubbin of soft tissue in the left thigh area.

The descent of the gonad may be impaired by its fusion with the spleen [Putschar and Manion, 1956]. Either a continuous cord remains between the two organs, or, in the discontinuous type, the cord is lost or never formed but an accessory spleen is found associated with the gonad. In the case described here, full gonadal descent had occurred. The cord was lying freely in the paracolic gutter. The location of the cord has been reported to be either anterior to the colon, anterior to the small bowel, or retroperitoneal [Walther et al., 1988].

The limb buds and the mandible also develop from the 6th to 7th embryonic week, and thus an association of splenogonadal fusion, amelia, and micrognathia may be the result of the causative factor acting around this time. Various forms of amelia are seen in association with splenogonadal fusion. However, in the review by Putschar and Manion [1956], only the case of Pommer closely resembles the present report in having almost complete tetra-amelia, micrognathia, and splenogonadal fusion of the continuous type.

It has been suggested that splenogonadal fusion of the discontinuous type is part of the accessory spleen spectrum. An accessory spleen has been described in one case of the Roberts-SC phocomelia syndrome, in whom PCS was also shown [Satar et al., 1994].

Tetraphocomelia vs. Tetra-Amelia

Roberts-SC phocomelia syndrome has marked variability in expression and there is speculation that this is the result of decreased cell growth occurring during various times in embryonic development [Tomkins and Sisken, 1984]; the disturbance in development would already be evident by the seventh embryonic week. In the review of 100 cases of Roberts syndrome, Van Den Berg and Francke [1993] reported the limb involvement to vary from a complete absence of arms and legs with rudimentary digits to mild growth deficiency in the limbs. Two patients had no phocomelia and in 11 patients only two limbs were deficient; most cases were less severe.

Tetra-amelia once was reported as part of the Roberts syndrome [Paulson et al., 1989]. Zimmer et al. [1985],

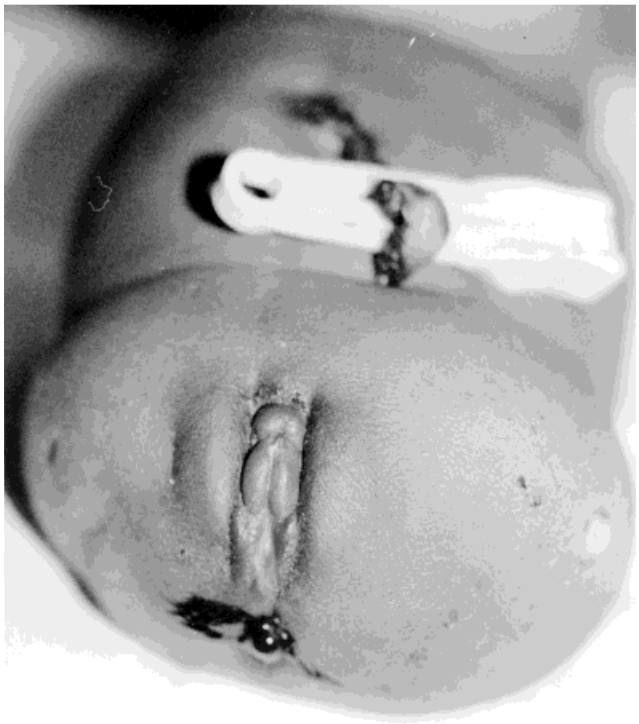

Fig. 4. Clitoromegaly.

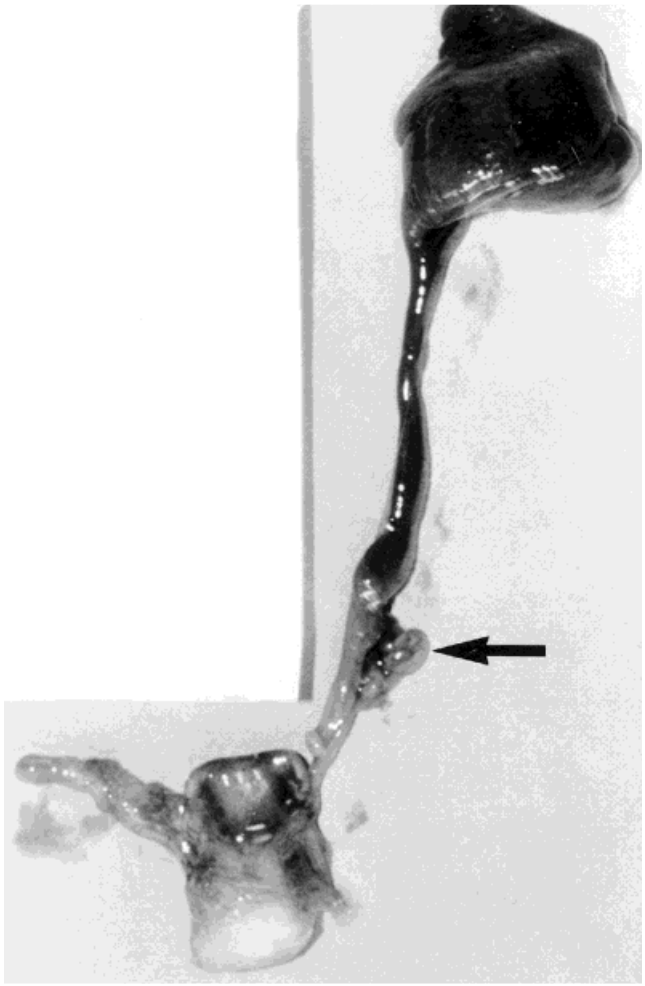

Fig. 5. The spleen attached to the left ovary (arrow).

in reporting a large family with a number of individuals with tetra-amelia, raised the question whether these cases were a variant of Roberts syndrome or a separate entity. On further discussion of this same family, Gershoni-Baruch et al. [1990] suggested that the cases may have extremely severe Roberts syndrome, although such a diagnosis was not favoured. These cases did not exhibit PCS as do 21% of all cases of Roberts syndrome [Van Den Berg and Francke, 1993]. Similarly, Başaran et al. [1994] could not confirm the prenatally suspected diagnosis of Roberts syndrome in their case with tetra-amelia, lung hypoplasia, heart defects, cleft lip and palate, and other anomalies as these were not all characteristic symptoms of the syndrome and as PCS as a diagnostic criterion was not present.

Zlotogora et al. [1993] argue that the absence of PCS in the case of Rosenak et al. [1991] excludes the diagnosis of Roberts-SC phocomelia syndrome. However Van Den Berg and Francke [1993] later reported that 21 out of 100 cases of Roberts syndrome had no PCS. Thus, the absence of this phenomenon is not an exclusion criterion. We propose that these cases may demonstrate severe expression of the Roberts syndrome even though PCS is not exhibited.

The phenotypic variability of Roberts syndrome does not correlate with the presence or absence of PCS. However, PCS is considered diagnostic when there is associated pre- and post-natal growth retardation, symmetrical limb reduction defects, and craniofacial malformations. The phenomenon of PCS was first described in 1974 by Freeman et al. in a typical case of Roberts syndrome. In this syndrome the PCS occurs in

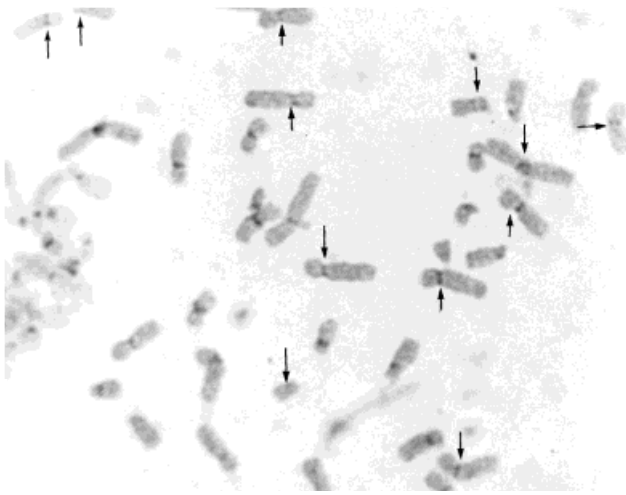

Fig. 6. Premature centromere separation (arrows).

most cells but mainly affects specific chromosomes (1, 9, 16, and Y, and the acrocentric chromosomes). PCS has been reported to be transmitted in an autosomal dominant fashion in a few families [Rudd et al., 1983]. However, in these cases all chromosomes in each of only a few cells displayed the phenomenon.

Reported cases of tetra-amelia show a wide range of combinations of limb deficiencies. In some there is limb deficiency, whereas in others there is total agenesis. The limb involvement may be symmetrical or asymmetrical. The case reported here has severe tetra-amelia. On clinical grounds it is not possible to decide whether this is a case of severe tetra-amelia, which is usually of sporadic occurrence, or whether the case is the severe expression of autosomal recessively inherited Roberts syndrome. The finding of PCS supports the latter.

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